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Intrinsic Brain Connectivity in Fibromyalgia is Associated with Chronic Pain Intensity

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Abstract

OBJECTIVE—Fibromyalgia (FM) is considered to be the prototypical central chronic pain syndrome and is associated with widespread pain that fluctuates spontaneously. Multiple studies have demonstrated altered brain activity in these patients. Our objective was to investigate the degree of connectivity between multiple brain networks in FM, as well as how activity in these networks correlates with spontaneous pain.

METHODS—Resting functional magnetic resonance imaging (fMRI) data in FM patients (n=18) and age-matched healthy controls (HC, n=18) were analyzed using dual regression independent component analysis (ICA) - a data driven approach used to identify independent brain networks. We evaluated intrinsic, or resting, connectivity in multiple brain networks: the default mode network (DMN), the executive attention network (EAN), and the medial visual network (MVN), with the MVN serving as a negative control. Spontaneous pain levels were also covaried with intrinsic connectivity.

RESULTS—We found that FM patients had greater connectivity within the DMN and right EAN (rEAN; $p<0.05$, corrected), and greater connectivity between the DMN and the insular cortex – a brain region known to process evoked pain. Furthermore, greater spontaneous pain at the time of the scan correlated with greater intrinsic connectivity between the insula and both the DMN and rEAN ($p<0.05$, corrected).

CONCLUSION—Our findings indicate that resting brain activity within multiple networks is associated with spontaneous clinical pain in FM. These findings may also have broader implications for how subjective experiences such as pain arise from a complex interplay amongst multiple brain networks.

Keywords

resting state fMRI; fcMRI; default mode network; fibromyalgia; executive attention network

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INTRODUCTION

Chronic pain disorders cause significant disability and dysfunction for patients and are particularly troublesome for researchers and clinicians alike. As pain is inherently a subjective sensation, clinicians and researchers must rely on patient self-report of pain severity. As such, the development of objective marker(s) that could simultaneously validate chronic pain symptoms and be used in elucidating underlying disease pathology would be of significant benefit. Recent neuroimaging studies have focused on identifying neural correlates of chronic pain in human patients (1,2), however this has been notoriously problematic because chronic pain is difficult to elicit in a controlled manner as it arises spontaneously and can fluctuate in magnitude (3).

Fibromyalgia (FM) is considered to be the prototypical central or “functional” chronic pain syndrome (4) and is associated with widespread pain. FM is also characterized by increased sensitivity to noxious and non-noxious stimuli (i.e. hyperalgesia and allodynia respectively) and augmented brain responses to experimental painful stimuli(5,6). While informative, these latter studies, which have looked at evoked experimental pain thresholds using brain imaging, provide little information regarding the underlying constituents of endogenous clinical pain. In fact, experimental pain measures only show modest correlations with self-reported clinical pain in this population (7).

Resting functional connectivity MRI is a recent adaptation of functional MRI (fMRI) that may be promising for associating spontaneous functional pain with specific brain network activity. This method examines intrinsic connectivity, which is defined as ongoing neural and metabolic activity that occurs in the resting basal state. This intrinsic or resting state of the brain actually demands the bulk of brain energy metabolism in comparison to the relatively small (<5%) fraction of energy metabolism demanded by stimulus-evoked activity (8). While the role of intrinsic brain connectivity has not been definitively resolved, it may be important for maintenance of synaptic connectivity such as the magnitude and extent of neuronal transmission between brain regions. Intrinsic connectivity also may involve information transfer between disparate brain regions comprising known primary sensory, executive, and associative networks (9). FMRI investigations of intrinsic connectivity networks (ICN), brain regions showing correlated activity when the participant is at rest, are conducted with subjects simply resting in the MRI scanner. These data can then be analyzed with independent component analysis (ICA) - a data driven analysis method that can isolate independent brain networks that have temporally correlated fMRI timeseries. These brain networks are thought to be connected synaptically since the fMRI signal between brain areas in these networks is correlated over time. Specifically, correlation in the ICN fMRI signal follows known structural monosynaptic and polysynaptic pathways (10,11), likely reflecting neurophysiologically meaningful activity (12).

While ICNs have been implicated as traits in several patient populations, the relationship of ICNs to state-dependent processes, such as chronic pain perception, remains largely unexplored. If intrinsic brain connectivity is found to correlate to the chronic pain state, it could suggest much-needed objective biomarkers for clinical pain perception and opens up several interesting avenues for research. Interestingly, the time scale of spontaneous pain fluctuation (seconds to minutes (13)) is on the same order as the low-frequency ICN intrinsic connectivity, providing additional rationale for investigating the association between the two.

While several ICNs have been identified in healthy subjects (14), two important networks related to cognition and potentially clinical pain are the default mode network (DMN) and executive attention network (EAN). The DMN (9,15) is a constellation of brain regions

thought to be engaged in self-referential thinking that are "deactivated" during various externally focused task conditions. Pain is known to influence both DMN response and as well as cognitive capacity. While acute experimental pain induces DMN deactivation in healthy subjects (16), chronic back pain is associated with mitigated DMN deactivation to visual attention tasks (17). The fronto-parietal EAN is a brain network that appears to be involved with cognitive processing for working memory and attention (18,19). FM patients are known to suffer concomitant cognitive deficits, which affect both working memory and attention processing (20), providing a rationale for evaluation of intrinsic connectivity in the EAN.

Given that [1.] DMN response may be disrupted in chronic pain patients, [2.] cognitive deficits specific to working memory and attention are common in FM patients (20), and [3.] accumulating evidence suggests that intrinsic brain connectivity may be state-dependent (21,22), we hypothesized that intrinsic DMN and EAN connectivity in FM patients would be altered and associated with spontaneous clinical pain report. In order to strengthen the specificity of our findings, we also examined intrinsic connectivity in the medial visual network (MVN) as a negative control, since dysfunction in this primary sensory network has not been noted in FM.

METHODS

Subjects and Data Collection

Data were collected from 36 female subjects, from two separate groups: 18 fibromyalgia (FM) patients (38.9 ± 10.8 years; $\mu \pm \sigma$) and 18 age-matched healthy control (HC) subjects (36.1±15.3 years, $p=0.53$). All participants gave written informed consent and the University of Michigan Institutional Review Board approved all study protocols.

FM patients in this study: 1) met the American College of Rheumatology criteria (23) for the diagnosis of FM for at least 1 year; 2) had continued presence of pain more than 50% of days; 3) were willing to limit the introduction of any new medications or treatment modalities for control of FM symptoms during the study; 4) were over 18 and under 75 years of age; 5) were female; 6) were right handed; and 7) were capable of giving written informed consent. FM participants were excluded if they: 1) had current use or a history of use of opioid or narcotic analgesics; 2) had a history of substance abuse; 3) had the presence of concurrent autoimmune or inflammatory disease such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, etc. that causes pain; 4) had concurrent participation in other therapeutic trials; 5) were pregnant and nursing mothers; 6) had severe psychiatric illnesses (current schizophrenia, major depression with suicidal ideation, substance abuse within two years); or 7) had current major depression. Depression in these patients was assessed with either the Hospital Anxiety and Depression Scale (HADS, 8 patients) or the Center for Epidemiologic Studies Depression Scale (CES-D, 10 patients). Categorization of FM patients with high depressive symptoms was defined as ≥ 8 for the HADS and ≥ 16 for the CES-D.

All HCs were: 1) between 18 and 75 years of age, 2) female, 3) capable of giving written informed consent, 4) right handed, and 5) willing to complete all study procedures. Exclusion criteria for HCs were: 1) having met the ACR criteria for FM; 2) having any chronic medical illness including psychiatric disorders (psychosis, schizophrenia, delusional disorder etc.); and 3) subjects who were pregnant.

Six minutes of resting state fMRI data were collected as the first functional scan run in the session. We used a spiral in-out gradient echo T2*-weighted BOLD pulse sequence (TR/TE=2000/30 ms, 180 volumes, 43 AC-PC aligned slices, voxel size=3.13 × 3.13 × 4.0 mm)

running on a 3T Signa EXCITE scanner (GE, Milwaukee, USA) equipped with a 8-channel head coil. Subjects were instructed to close their eyes and to rest comfortably during the functional scan without moving or falling asleep. Structural data were also collected using a SPGR pulse sequence (TE = 5.5 ms, TR = 14 ms, TI = 300 ms, flip angle = 20 degrees, NEX = 1, 124 contiguous axial slices, voxel size=1×1×1.5 mm).

Prior to scanning, subjects were asked to rate the intensity of their fibromyalgia pain on a verbal analog scale of 0 to 10, where 0 is equivalent to “no pain present,” and 10 is equivalent to “the worst pain they could imagine.”

Physiological data were collected simultaneously to the fMRI data, as cardio-respiratory fluctuations are known to influence fMRI intrinsic connectivity estimation within several brain networks (24,25). Cardiac data were acquired using an infrared pulse oximeter (GE, Milwaukee, USA) attached to the right middle finger. Respiratory volume data were acquired using an MR-compatible belt (GE, Milwaukee, USA) placed around the subject’s ribcage.

Functional MRI Data Analysis

Data analysis was performed using the validated FSL (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl) software package. Data were corrected for motion artifact, compensating for any head movements using a linear (affine) transformation procedure (FSL-MCFLIRT). Brain extraction was performed on functional data using the brain extraction tool (FSL-BET). Functional data were smoothed using a Gaussian kernel of FWHM 5 mm; and high-pass temporal filtering (f = 0.006Hz) was also performed. The latter was done since [1] we wanted to remove very low frequency scanner drift artifacts and [2] our ICNs show peak power at higher frequencies (~0.03Hz) (26,27).

The within- and between-subject resting fMRI data analysis was performed using ICA through Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC, an FSL tool) and a previously validated dual regression approach (28). This technique allows for voxel-wise comparisons of resting state functional connectivity by first temporally concatenating resting fMRI data from all subjects, followed by back-reconstructing the group ICNs for individual subjects, which are then used for within- and between-subject group and difference maps. This technique has been found to have moderate to high test-retest reliability in previous studies (29). Functional data were first projected to standard Montreal Neurological Institute (MNI) space using structural/functional linear (affine) co-registration (FSL-FLIRT), and non-linear structural/template co-registration using FMRIB’s Nonlinear Image Registration Tool (FNIRT). These BOLD functional data (180 volumes for each subject) were then concatenated in time across all subjects, creating a single 4D dataset. We then applied probabilistic Independent Component Analysis (pICA, MELODIC, FSL) to identify global, distinct (independent) patterns of functional connectivity existent in the entire subject population (covering both FM patients and HCs). We limited the number of independent components (ICs) in this step to 25. This was done to limit IC splitting into subcomponents, as recommended by Filippini and Smith (28). From this pool of 25 ICs, ICNs of interest were selected using our goodness-of-fit method (21), with previously defined templates generously provided by Beckmann et al. (14). Briefly, the best-fit component was selected by calculating the average z-score of voxels both inside and outside of the template then selecting the component maximizing the inside - outside difference. This process was completed for the following networks of interest: the DMN, EAN, and the medial visual network (MVN) - a control network with less direct association to the chronic pain state. Characteristically, the DMN includes the inferior parietal lobule (IPL, BA 40, 39), the posterior cingulate cortex (PCC, BA 30, 23, 31) and precuneus (BA 7), areas of the medial frontal gyri (BA 8, 9, 10, 47), the hippocampal

formation, and the lateral temporal cortex (BA 21) (30). The EAN is typically split by ICA into a right and left lateralized network, and includes the dorsolateral prefrontal cortex including (roughly) the frontal eye fields (BA 4, 6, 8) and posterior parietal regions overlapping the superior parietal lobule (SPL, BA 7) and intraparietal sulcus (iPS, BA 7, 40) (14,18). The MVN primarily includes bilateral VI in the calcarine sulcus and medial parastriate regions including the lingual gyrus (BA 17,18) (14).

In the next stage of the dual regression approach, the spatial IC maps identified from the population data were used as a spatial regressor in a general linear model (GLM) of the subject's resting fMRI data. Hence, this model was used to find the subject-specific temporal dynamics within the 25 ICNs defined above. The time-series for each component were then variance normalized (subtracting the mean and dividing by the standard deviation) and used as a temporal regressor in a GLM of the subject's resting fMRI data. In order to limit any residual shared variance with non-neuronal (e.g. cardio-respiratory physiological) processes, this GLM also included temporal regressors from white matter and ventricular regions (similar to (11) and others), as well as regressors representing cardiac and respiratory variability defined by convolving the heart rate time series and respiratory variations with appropriate cardiac and respiratory transfer functions, respectively, as defined and suggested by Chang et al. (31) and Birn et al. (32). This allowed us to estimate subject-specific spatial maps for each component. These maps were then input into our higher level analyses (see below).

Group analysis was performed to evaluate intrinsic brain connectivity differences between our two groups (FM and HC), as well as how this intrinsic connectivity covaries with spontaneous pain intensity in FM patients. Group main effect maps for both FM and HC, as well as a difference map (unpaired t-test for FM – HC) were calculated for our ICNs of interest (DMN, EAN, MVN). Both analyses used FMRIB's Local Analysis of Mixed Effects (FLAME), which uses Markov Chain/Monte Carlo sampling to estimate the true random-effects component of the between-subject mixed effects variance and degrees of freedom at each voxel. The result of the unpaired t-test difference map was threshold at $p < 0.05$, cluster-corrected for multiple comparisons.

In order to more closely link intrinsic connectivity with the chronic pain state in FM patients, an analysis of covariance (ANCOVA) was also performed for ICNs demonstrating significant differences in intrinsic connectivity between FM patients and HC subjects. The covariate of interest was the spontaneous pain score reported by the patients immediately prior to the resting scan. This pain score was adjusted for age, as [1] age is known to influence ICN connectivity (33), and [2] there was a significant correlation between spontaneous pain and age ($r=0.61$). The ANCOVA was performed using a mixed effects model, and was threshold at $p < 0.05$, cluster corrected for multiple comparisons.

RESULTS

Resting fMRI data were collected from all 36 female subjects. Clinical pain intensity at the time of the scan (0–10 VAS) was also collected from the FM patients and ranged from 0.0 to 8.1 (4.8 ± 2.4; $\mu \pm \sigma$). As part of our dual regression probabilistic ICA approach, we identified 25 independent components (IC) in the temporally concatenated 4D population dataset, from which the DMN, EAN, and MVN were robustly defined (see group maps in Figure 1). As typically noted in past studies (14,34), the EAN was split into two lateralized networks, the right EAN (rEAN) and left (lEAN).

Intrinsic Brain Connectivity for FM compared to HC

Of the ICNs evaluated, intrinsic connectivity within the DMN and right EAN (rEAN) demonstrated significant differences between FM patients and HCs. Notably, for the DMN, the regional differences between the two groups were uniformly driven by greater positive DMN connectivity for FM patients compared to HC (Figure 1, Table 2). FM patients demonstrated greater intrinsic DMN connectivity to brain regions outside of the classical boundaries of the DMN, namely the left anterior (aIns), middle (mIns), and posterior (pIns) insula and left secondary somatosensory cortex (SII). No brain regions were more correlated to the DMN for HC compared to FM.

Connectivity differences between FM and HC were also noted for the rEAN (Figure 1, Table 2). Specifically, FM patients demonstrated greater intra-network connectivity within the right iPS. No brain regions were more correlated to the rEAN in HC compared to FM. Moreover, no differences between FM and HC were found for the left EAN or the MVN, our control network.

Covariation between Intrinsic Connectivity and Spontaneous Pain

An ANCOVA was performed with subjective pain intensity at the time of the scan serving as the covariate of interest. This analysis more closely links intrinsic brain connectivity with the chronic pain state. For the DMN, this analysis demonstrated that greater spontaneous pain at the time of the fMRI scan was associated with greater DMN connectivity to the right middle and anterior insula (Figure 2, Table 3). A positive covariation with spontaneous pain was also noted in the cerebellum, dorsolateral prefrontal (dlPFC) and subgenual anterior cingulate (sgACC) cortices.

For the rEAN, greater spontaneous pain correlated with greater intrinsic connectivity to the right anterior and left middle and posterior insula (Figure 3, Table 3). A positive correlation with spontaneous pain was also noted between the rEAN and putamen, while a negative correlation (greater rEAN connectivity for lower pain levels) was noted for the hippocampus, periaqueductal gray (PAG), nucleus cuneiformis and pontine raphe.

In order to test for the influence of depression on any of our pain-focused results, we also evaluated if FM patients with high depression symptoms had greater ICN connectivity to any of the brain regions implicated above. Based on our criteria, 7 patients had high depressive symptoms, while 11 did not. We found no significant differences (all $p>0.2$) between these two FM patient sub-populations for ICN connectivity to ROIs noted in either the FM versus HC difference maps or ANCOVA results.

DISCUSSION

We present the first direct evidence of linkage between elevated intrinsic brain connectivity and spontaneous pain intensity in FM. We applied ICA to resting state fMRI data and found that FM patients had greater connectivity within the rEAN and between the DMN and the insular cortex a brain region linked to evoked pain processing. Furthermore, our data directly links spontaneous pain report at the time of the scan to the degree of both rEAN and DMN connectivity to the insula. Our findings have implications for underlying brain mechanisms of endogenous clinical pain in FM, potentially pointing towards “markers” for disease progression. More broadly, these findings have implications for how subjective experiences such as pain arise from a complex interplay amongst multiple brain networks.

Our results strongly implicate the insular cortex as being a key node in the elevated intrinsic connectivity in FM patients. Patients demonstrated greater DMN connectivity to the left anterior, middle, and posterior insula. Furthermore, FM participants with greater

spontaneous pain levels displayed increased intrinsic connectivity between both the DMN and rEAN and insular cortex. Many studies have found insular involvement in the multidimensional (sensory, affective, cognitive) pain state. This insula is one of the most commonly activated brain regions in neuroimaging studies of acute experimental pain (35). The posterior insula has been associated with sensory intensity encoding (36), while the anterior insula may be more strongly related to affective dimensions of pain, such as anticipatory anxiety related to pain (37). However, the insula does not just process pain signals, and has been implicated in multiple association processes related to both interoceptive (38) and exteroceptive salience (18). In fact, it has been hypothesized that the insula integrates subcortical homeostatic information, such as that arising from a pain state (39), into a higher-order cognitive and affective conscious state of awareness (40). Our data supports this view as ratings of spontaneous pain were correlated to increased insular connectivity in brain networks (DMN, EAN) known to support cognition.

Intrinsic connectivity between the posterior insula and DMN areas such as the PCC has been shown to exist even in healthy subjects (41). Substantial positive DMN connectivity to the posterior insula was also noted for both FM and HC in our analysis. This suggests that existing links between the DMN and insula may be hyperactive in FM patients. This hyperactive connectivity has been suggested by proton magnetic resonance spectroscopy (H-MRS) studies in FM patients' where posterior insula glutamate levels appear to be elevated (42). Future studies should also explore increased glutamate concentrations within the DMN, as we found increased intrinsic DMN connectivity for FM patients. In addition, greater DMN-insular resting connectivity could lead to altered DMN response to external sensory input for FM, something that was found for chronic low back pain patients responding to cognitive/visual tasks (43).

It is also interesting to speculate that pain related reorganization of ICNs associated with working memory and attention (EAN) provides a potential neurobiological mechanism to the known cognitive deficits in FM patients (for review of FM-related dyscognition see (20)). Perhaps not-coincidentally, these deficits appear to be focused on working memory and attention, and are particularly exacerbated with increasing distraction. Notably, FM patients' cognitive deficits correlate more with their pain than with psychiatric co-morbidities (e.g. depression, anxiety, sleep disruption), as shown by a recent study by Dick et al. (44). Our results indicate that insula-rEAN connectivity for FM increases with increasing levels of spontaneous pain. Interestingly, PAG-rEAN connectivity *decreases* with increasing pain, consistent with the hypothesis that cognitive controls for descending inhibition (anti-nociception) might modulate FM pain levels. We suggest that the insula, which is intimately involved with multidimensional aspects of pain processing, becomes more hyper-connected to the rEAN with increasing pain levels for FM, diverts resources away from normal rEAN functioning, thereby leading to deficits in working memory and attention.

We found altered intrinsic connectivity in the right, but not left, EAN. ICA commonly separates the EAN into a right and left lateralized network (14,34). Laterality in working memory and attention tasks has been noted in previous neuroimaging studies (45) and lesions of the iPS typically result in spatial attention deficits when localized to the right side (46). This laterality corroborates our suggestion that altered intrinsic rEAN connectivity may play a role in dyscognition in FM patients. Future studies should explore the significance of right, versus left, EAN connectivity in FM patients.

Another interesting finding was that the differences between FM and HC groups in DMN and EAN connectivity were driven entirely by the FM group and not HC. While this result could indicate that the observed differences were either the consequence or the cause of

lingering chronic pain, it certainly supports the growing body of evidence that FM, and likely other chronic pain syndromes, are accompanied by altered brain neurophysiology. Moreover, this result was qualitatively similar to recent reports of altered ICN connectivity in patients with other forms of chronic pain (47). Specifically, Cauda et al. reported enhanced resting DMN connectivity within DMN component regions (precuneus, IPL), sensorimotor (bilateral thalamus and insula), and cognitive / evaluative pain modulatory regions (dlPFC). However our findings substantially add to this inter-group comparison, as we found that the degree of DMN connectivity was associated with state-specific pain report at the time of the scan - an important finding as it specifically links intrinsic functional connectivity to the chronic pain state. The specificity of our results was buttressed by the fact that a control brain network, the MVN (not previously implicated in FM pathology), did not display altered intrinsic connectivity. Thus, our findings of altered brain connectivity appear to not be widespread, but are localized to DMN and rEAN intrinsic connectivity networks.

Other neuroimaging approaches have also attempted to evaluate the brain correlates of spontaneous clinical pain. Positron emission tomography (PET) with opioid binding agents has found that FM patients have decreased binding potential within the nucleus accumbens, which correlated with increasing spontaneous pain (48). An H-MRS study found that reductions in resting glutamate concentration in the posterior insula are associated with reductions in clinical FM pain report (49). Finally, continuous on-line patient report of spontaneous pain fluctuation was used to guide fMRI statistical analysis and found that fMRI signal in the medial-prefrontal cortex (MPFC) correlates with spontaneous pain intensity (1). Our results add to this growing literature on neural correlates of chronic pain. The MPFC is a cardinal node of the DMN, and our results point to increased intrinsic DMN connectivity to the insula, with increasing connectivity directly correlated with increasing levels of spontaneous clinical pain in FM patients.

There are a number of limitations to our findings that should be discussed. First, our results were derived strictly from FM patients and may not generalize to other chronic pain states, a possibility we are currently evaluating. However qualitatively similar findings have been observed in neuropathic pain patients (47), thus our results likely do have some generalizability. Furthermore, all of our participants were female, leaving open the possibility that FM pathophysiology may in fact be different for male patients. Finally, some of our FM patients were taking medications during the time of the scan (see Supplementary Table 1), thus some findings may have been influenced by pharmacological modulation of neural connectivity. For ethical reasons, subjects were not asked to titrate down their existing pain medications for this study. However, none of our patients were taking opioid medications, and as the effects of other (e.g. SSRI, SNRI) medications on intrinsic brain connectivity are unknown, they should be explored in future studies. Larger studies, which could group participants by medication usage, can also address this issue.

In conclusion, we find direct evidence of disrupted intrinsic connectivity within multiple brain networks in FM patients. These findings are in agreement with other brain imaging results which indicate that individuals with FM have altered brain function (5,6,42,48). Emerging evidence suggests that FM pain may be mediated by central nervous system hyperexcitability rather than peripheral pathology. Our results clearly show that individuals with FM have greater connectivity between multiple brain networks and the insular cortex – a brain region previously linked with evoked pain processing and hyperexcitability in FM. Our data also demonstrate that intrinsic connectivity to the insula is directly associated with increasing spontaneous pain. Hence, our approach represents a novel step forward in finding the neural correlates of spontaneous *clinical* pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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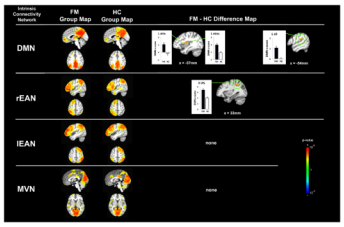

Figure 1.

ICN Group and Difference Maps. Group maps for HC and FM demonstrate the expected anatomical scope of the canonical DMN, EAN, and MVN for both groups, with the EAN split into a right and left lateralized network. Difference maps contrasting FM versus HC demonstrated that FM patients had greater intrinsic DMN connectivity to several brain regions outside the DMN but known to process evoked pain (insula). FM also demonstrated greater rEAN connectivity within this ICN (iPS). n.b. SII = secondary somatosensory cortex, iPS = intraparietal sulcus.

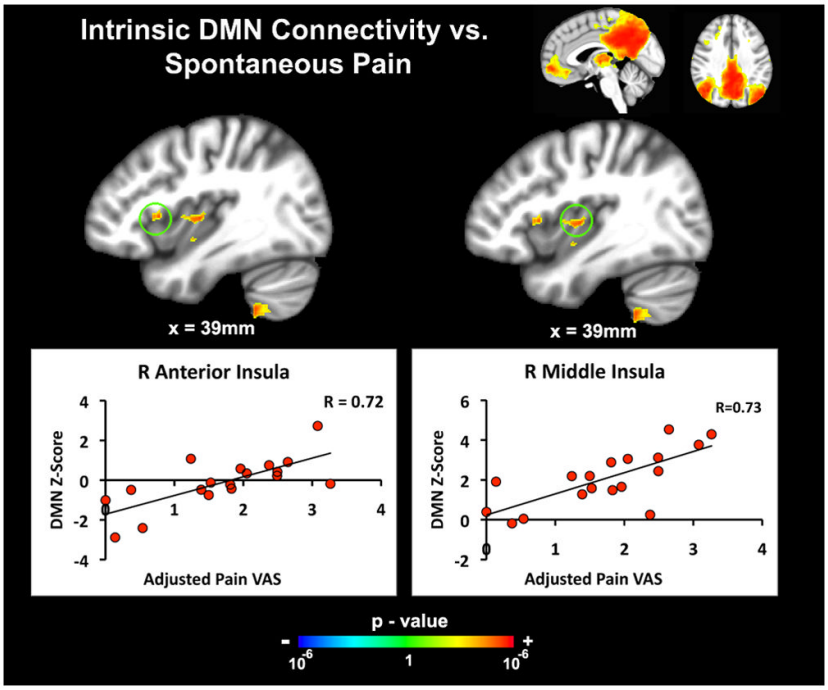

Figure 2.
Covariation between DMN connectivity and age-adjusted spontaneous pain. Greater spontaneous pain intensity correlated with linearly increasing intrinsic DMN connectivity to the right middle and anterior insula.

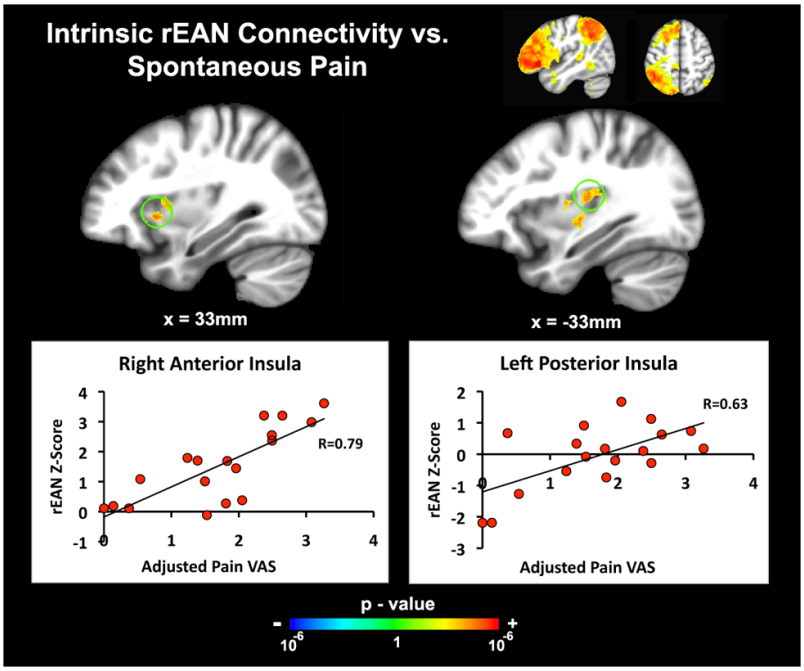

Figure 3.
Covariation between rEAN connectivity and age-adjusted spontaneous pain. Greater spontaneous pain intensity correlated with linearly increasing intrinsic rEAN connectivity to the right anterior insula and left posterior insula.

Table 1

Glossary of Relevant Terms

Default Mode Network (DMN)	This brain network is a constellation of brain regions thought to be engaged in self-referential thinking. This network is "deactivated" during various externally focused task conditions – i.e. it is more active at rest. Anatomically it includes the inferior parietal lobule, the posterior cingulate cortex and precuneus, areas of the medial frontal gyri, the hippocampal formation, and lateral temporal cortex.
Dual Regression Independent Component Analysis (ICA)	This technique to analyze resting fMRI data allows for the estimation of resting state, or intrinsic, functional connectivity networks. FMRI data from each subject are combined and evaluated with ICA. These group intrinsic connectivity networks (ICNs) are then used to find individual ICNs specific to each subject, which are then used for within- and between-subject analyses.
Executive Attention Network (EAN)	This brain network is involved with cognitive processing for working memory and attention. It is anatomically comprised of frontal and parietal lobe regions including the dorsolateral prefrontal cortex (roughly the frontal eye fields) and posterior parietal regions overlapping the superior parietal lobule and intraparietal sulcus.
Intrinsic Connectivity Network (ICN)	Networks of different brain regions that are connected to each other in a resting basal (as opposed to a stimulus-evoked) state.
Medial Visual Network (MVN)	This brain network includes primary visual processing areas (VI) on both hemispheres and anatomically includes regions along the calcarine sulcus and lingual gyrus.
Spontaneous Clinical Pain	Clinical fibromyalgia pain fluctuates spontaneously over time. Spontaneous pain was reported by our subjects at the time of the MRI scan, and was used to guide our statistical analysis.
State-specific	Pertaining to a state of mind that the subject is in during the fMRI brain scan.
Synaptic Connectivity	Brain regions connected to one another through at least one synapse between two neurons. Information is exchanged between these regions.

Table 2

FM - HC Difference Maps for Intrinsic Connectivity

			Location (MNI)					
	Side	**Size (mm^2)**	**X**	**Y**	**Z**	**FM-HC Z-score**	**FM**	**HC**
Default Mode Network (DMN)								
anterior insula	L	552	−34	6	10	3.33	1.04±1.05	−0.12±1.15
middle insula	L	848	−36	−8	18	4.08	1.98±0.96	0.92±0.81
posterior insula	L	704	−46	−30	22	3.25	1.80±0.95	0.75±0.93
SII	L	1480	−52	−34	28	3.88	1.07±0.72	0.02±0.53
right Executive Attention Network (rEAN)								
intra-parietal sulcus	R	1032	30	−44	44	3.59	3.46±1.28	2.00±0.90
left Executive Attention Network (lEAN)								
none								
Medial Visual Network (MVN)								
none								

Table 3

Covariation between Intrinsic Connectivity and Spontaneous Pain

			Location (MNI)					
	Side	**Size (mm^2)**	**X**	**Y**	**Z**	**Z-score**	**Low Pain**	**High Pain**
Default Mode Network (DMN)								
anterior insula	R	464	42	14	8	3.29	−1.72±0.81	0.55±1.32
middle insula	R	688	38	−10	6	3.43	0.80±0.47	3.06±0.49
dlPFC	R	736	60	−14	34	3.09	−0.84±1.44	1.07±0.99
cerebellum	L	808	−22	−74	−40	3.86	−1.37±0.49	0.33±0.71
subgenual cingulated	R	248	6	26	−12	3.75	−1.11±0.98	1.12±0.30
right Executive Attention Network (rEAN)								
anterior insula	R	816	28	26	−6	3.78	0.57±0.48	2.72±0.95
middle insula	L	400	−36	−8	10	2.88	−1.28±1.11	1.14±0.89
posterior insula	L	336	−32	−20	14	2.79	−1.17±1.37	0.24±0.51
hippocampus	R	160	18	−20	−18	−3.07	1.39±0.86	−0.10±0.48
putamen	R	408	24	16	−6	3.12	−0.02±0.47	1.80±1.11
PAG	L	256	−2	−26	−10	−3.58	1.45±0.91	−0.52±1.68
nucleus cuneiformis	R	320	12	−26	−16	−3.40	1.07±1.32	−0.63±0.70
pontine raphe	L	496	−2	−30	−28	−4.15	1.55±0.56	0.02±0.63

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